PATENT
Attorney Docket No.: 02307O-115611US
Client Ref. No.: 2000-094-3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 4011
Deanna L. KROETZ et al.	Examiner: Brian Yong Kwon
Application No.: 10/694,641	Technology Center/Art Unit: 1614
Filed: October 27, 2003	DECLARATION OF DR. BRUCE HAMMOCK
For: INHIBITORS OF EPOXIDE HYDROLASES FOR THE TREATMENT OF HYPERTENSION	
Customer No.: 20350	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, BRUCE D. HAMMOCK, PH.D., hereby declare as follows:

1. I received a Ph.D. from the University of California at Berkeley in 1973. I have been a member of the faculty of the University of California since 1980 and have been a full Professor since 1983. I have held the title of Distinguished Professor since 2003. A summary of my employment and professional honors is set forth on the attached "Biographical Sketch."

2. I was elected to membership in the National Academy of Sciences in 1999.

3. I am the author or a co-author of over 600 publications in the scientific literature. Some 240 of my publications concern epoxide hydrolases and their activity and role in lipid metabolism. Many of my publications have focused in particular on studying the activity of the enzyme soluble epoxide hydrolase ("sEH") and the effects of inhibiting the ability of sEH to hydrolyse epoxides. The attached "Biographical Sketch" sets forth my most recent publications in the areas of sEH metabolism and inhibition. The more complete list of my publications relating to epoxide hydrolases is currently 17 pages long; it is available on the internet and can be viewed by entering "www." followed by "biopestlab.ucdavis.edu/BIB-EH.htm."

4. I am an inventor named on the captioned application. I understand the Office Action dated December 29, 2005, rejects the claims as anticipated by compounds set forth in two references, Ichihara, JP 07304755 (hereafter, "Ichihara"), and Blum, U.S. Patent No. 5,962,455 (hereafter, "Blum"). I understand that the Action states that both Ichihara and Blum teach compounds that fall within Formula I for treatment of hypertension. I understand that the Action states that neither reference states that the compounds it discloses are inhibitors of soluble epoxide hydrolase, but that this activity would be inherent in the compounds since they read on the Formula.

5. I have reviewed the structures of the compounds disclosed by Ichihara and the compounds disclosed by Blum. I disagree with the Action's contention that the compounds disclosed by either of these references would function to significantly inhibit sEH (hereafter, "sEH") at physiologically relevant concentrations. (I put this qualification in since many otherwise inactive compounds are capable of inhibiting an enzyme's activity if present at concentrations beyond those that can be achieved *in vivo*.)

6. I note that the subject patent application, which has priority back to 1999, contains data on the activity of over 100 compounds in inhibiting human sEH. My laboratory

has now investigated the structure activity relationships ("SAR") of over 2000 compounds with regard to the ability of these compounds to inhibit human sEH, and have crystal structures of both the murine and the human sEH enzyme bound to selected inhibitors. As a result of these studies, we can now predict with a high degree of confidence what urea-based compounds will inhibit human sEH and which will not. As a result of these studies, I can predict that the compounds disclosed by Ichihara and by Blum will not significantly inhibit human sEH at physiologically relevant concentrations.

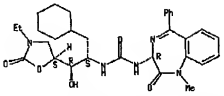
7. As an initial matter, although many compounds having a urea, amide or carbamate in them are good inhibitors, the presence of a urea, amide or carbamate is not sufficient. Urea by itself, for example, does not inhibit sEH at millimolar concentrations, nor do simple 1,3 di, tri, or substituted ureas such as diethyl and dipropyl urea.

8. With regard to the urea-based compounds disclosed by the references, our studies have shown that bulky or polar groups, or both, near the urea result in compounds that do not inhibit sEH. Based on the crystal structure, we can see that bulky groups are simply too large to fit into the active site. One needs active groups on both sides, so even if a naphthalene or quinoline show marginal activity as a substituent on one side, the other side must also be active.

9. I will turn first to the specific compounds which I understand the Examiner identified by registry number as being disclosed by Ichihara and by Blum, respectively. I will set forth below the registry number and structure of each of these specific compounds, and then my comments on the predicted activity of the compound on inhibiting the ability of sEH to hydrolyze epoxides in light of our SAR studies. I will then briefly comment on the activity of the other compounds disclosed by the references but not specifically identified by the Examiner as anticipating the claims.

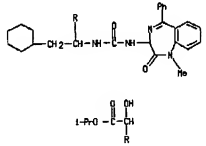
10. The following are the compounds identified to me as corresponding to the registry numbers cited by the Action as disclosed by Ichihara, and my comments on them.

A. RN 174398-90-4



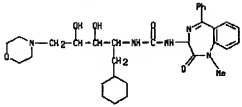
On the left side of the urea, the R group is too big and there is a polar group too close to the NH of the urea. The group to the right of the urea also has polar residues too close to the urea. Even with a highly potent group on the right side of the urea, the group on the left side would preclude activity. The crystal structure of the sEH enzyme shows a very hydrophobic catalytic tunnel except for very specific locations. Accordingly, I predict that this compound would be inactive as an inhibitor of sEH.

B. RN 174398-91-5



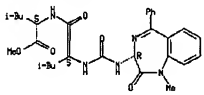
The group to the right side of the urea is too bulky and the R groups on both sides of the urea have polar groups too close to the urea. Accordingly, I predict that this compound would be inactive as an inhibitor of sEH.

C. RN 174398-92-6



The group to the left side of the urea has a diol that will kill activity. The R group to the right of the urea is too large and too polar. Accordingly, I predict that this compound would be inactive as an inhibitor of sEH.

D. RN 174398-93-7



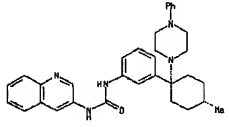
Once again, the groups to either side of the urea are too large and too bulky. Accordingly, I predict that this compound would be inactive as an inhibitor of sEH.

11. Ichihara also presents a 2 page table on pages 736 and 737, setting forth a number of compounds that appear to set forth various substituents to positions identified by a general structure on page 735. The structure on page 735 shows a 7 membered, heterocyclic ring with a substituted carbon next to the L1 substituent. The table shows that most of the compounds have a carbonyl in the L1 substituent. These compounds will be inactive as sEH inhibitors because the 7-membered unsaturated ring will not fit into the active site. Compound 10 does not have a carbonyl in L1 and thus does not fit into Formula I. If the R group on the carbon alpha to the carbonyl (of the compounds containing a carbonyl) were H, if the compounds

were not cyclic, and if the other R groups were right, one could conceive that a compound in this series could be active. Even then I would anticipate at most very weak activity. The general structures provided suggest that Ichihara is are targeting very different molecules and that the compounds Ichihara suggests for targeting those molecules would be inactive as inhibitors of the soluble epoxide hydrolase.

12. The following are the compounds identified to me as corresponding to the registry numbers cited by the Action as disclosed by Blum.

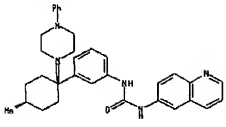
A. RN 202472-67-1



• 3 HCl

There is a slight chance the group on the left of the urea would yield activity with the correct substituents on the other side. However, the activity should be mediocre to poor. The group on the right is too large. I predict as well that the heterocycle will be far too polar. Accordingly, I predict that this compound would have poor to no activity as an inhibitor of sEH.

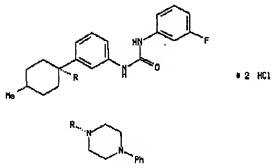
B. RN 202472-68-2



• 3 HCl

This compound is similar to the one discussed in item A, above, except that the sides are reversed. For the same reasons as set forth with respect to the preceding compound, I predict that this compound would have poor to no activity as an inhibitor of sEH.

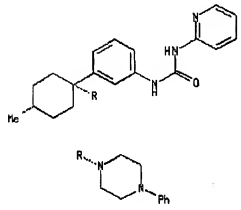
C. RN 202472-69-3



• 2 HCl

There is a chance that this compound could be of mediocre activity. The meta fluorophenyl substituent is active, but much less active than para substitutents. A simple di phenyl urea is of moderate activity as an sEH inhibitor. By having the branched carbon with both a methylcyclohexyl and a morpholino group, we have a massive bulk that would fit poorly into the crystal structures that we have developed.

D. RN 202472-70-6



My comments related to this compound are similar to the one immediately above. A simple di phenyl urea is of moderate activity as an sEH inhibitor. However, we have replaced a phenyl by a number of pyridine derivatives as shown on the right side of this molecule. They reduced biological activity dramatically. In particular this ortho substituted pyridine places a N too close to the catalytic site, killing its activity. By having the branched carbon with both a methylcyclohexyl and a morpholino group, we have a massive bulk that would fit poorly into the crystal structures that we have developed.

13. With regard to the compounds disclosed by Blum but not specifically cited by the Examiner, the general structures are quite broad so my comments will be correspondingly general. The comments I made about the specific compounds above can be generalized by noting that a polar group closer to the urea carbonyl than about 6 angstroms will eliminate the compounds from having activity as an inhibitor of sEH. This observation precludes many of the Blum compounds from having activity as inhibitors of sEH. Many of the compounds listed in the general structures have R and R' groups on the 1 and 3 positions of the urea that will not confer activity. The majority of the general structures disclosed in Blum have very large and

branched chain groups close to the urea which would dramatically reduce affinity for the enzyme. None of them have structures that would lead me to expect that they would inhibit sEH at physiologically relevant concentrations. These compounds were designed to bind to the neuropeptide Y1 receptor, which of course has its own very specific properties. One would be very surprised if a similar structure activity relationship was observed between a peptide receptor and an enzyme dealing with highly lipophilic fatty acid oxides.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

30 May 06
Date

Dr. Bruce D. Hammock

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